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Abstract

Objective: The past decades have seen a surge in stimulant prescriptions for the treatment of attention-deficit/hyperactivity disorder (ADHD). Stimulants acutely alleviate symptoms and cognitive deficits associated with ADHD by modulating striatal dopamine neurotransmission, and induce therapeutic changes in brain activation patterns. Long-term functional changes after treatment are unknown, as long-term studies are scarce and have focused on brain structure. In this observational study (2009-2012), we investigated associations between lifetime stimulant treatment history and neural activity during reward processing.

Method: Participants fulfilling DSM-5 criteria for ADHD (N=269) were classified according to stimulant treatment trajectory. Of those, 124 performed a monetary incentive delay task during magnetic resonance imaging, all in their non-medicated state ($n_{early\&intense}$=51; $n_{late\&moderate}$=49; $n_{early\&moderate}$=9; n_{naive}=15; mean age=17.4 years, range 10-26 years). Whole-brain analyses were performed with additional focus on the striatum, concentrating on the two largest treatment groups.

Results: Compared to the 'late-and-moderate' treatment group, the 'early-and-intense' treatment group showed more activation in the supplementary motor area and dorsal anterior cingulate cortex (SMA/dACC) during reward outcome (cluster size=8696 mm^3; $p_{CLUSTER}$<0.001). SMA/dACC activation of the control group fell in between the two treatment groups. Treatment history was not associated with striatal activation during reward processing.

Conclusion: Our findings are compatible with previous reports of acute increases of SMA/dACC activity in individuals with ADHD after stimulant administration. Higher SMA/dACC activity may indicate that patients with a history of intensive stimulant treatment, but currently off-medication, recruit brain regions for cognitive control and/or decision-making upon being rewarded. No striatal or structural changes were found.

Introduction

Stimulant treatment is the medical intervention of first choice for children and adolescents with attention-deficit/hyperactivity disorder (ADHD). The past decades have seen a surge in stimulant prescription rates.[1] Alleviation of symptoms and cognitive deficits associated with ADHD appears – in general – not to last after medication is discontinued, and there is little evidence of long-term improved functioning.[2-4] The absence of conclusive evidence regarding potential long-term effects of stimulant treatment, either positive or negative, has unsettled parents, patients, and society at large.

Studies of long-term stimulant treatment effects on brain structure have yielded mixed results. Two meta-analyses found that striatal volume was more reduced in patients compared to controls when the ADHD sample included more treatment-naive patients,[5,6] suggesting that striatal volume reduction observed in ADHD is driven by untreated rather than stimulant-treated patients. However, a large-scale longitudinal study, which employed the optimal design for the study of long-term treatment effects, did not find such treatment effects,[7] nor did previous analyses in our own sample.[8,9]

The literature on long-term treatment effects in the human brain has, with few exceptions, focused on brain structure, while studies of acute stimulant effects focused on brain activation patterns. A single dose of methylphenidate has repeatedly been found to alter brain activation patterns in ADHD patients; case-control differences in blood-oxygen level dependent (BOLD)-response to cognitive/motivational tasks became smaller or disappeared when patients were on stimulant medication.[10] Little is known about whether acute functional changes translate into long-term functional changes as well. Adults with a history of untreated childhood ADHD showed blunted ventral-striatal activation compared to controls when exposed to emotional pictures, whereas adults with a history of ADHD who had received stimulant treatment during childhood did not.[11] During reward processing, the same group of treatment-naive adults showed lower insula activation compared to controls and childhood stimulant-treated adults.[12] These findings may suggest enduring functional therapeutic changes. In a meta-analysis of attention tasks, striatal activity was particularly reduced in studies including mostly stimulant-

naive patients.[13] Radio-ligand studies, however, have reported exacerbated rather than attenuated deficits in striatal dopamine neurotransmission after long-term stimulant treatment in adults with ADHD.[14,15] Summarizing, stimulant treatment may be associated with persistent changes in brain activation patterns and/or dopamine metabolism, but the evidence is very limited and it remains unclear to what extent such changes may be therapeutic or disadvantageous.

The striatum is of particular interest when studying stimulant treatment effects in ADHD. Reduced striatal volumes,[5,6] lower striatal activity during reward anticipation and higher striatal activity during outcome of reward[16-18] have repeatedly been found in ADHD. Moreover, the striatum is rich in dopamine transporters, an important molecular target of stimulant treatment. Hence, long-term stimulant treatment effects may be expected to occur in the striatum. However, acute stimulant-induced changes in activation patterns have also been reported in supplementary motor areas (SMA), frontal cortex, anterior and posterior cingulate cortex, and precuneus cortex.[e.g.,19-21]

We investigated associations between lifetime stimulant treatment history and neural activity during reward processing, using magnetic resonance (MRI) data from a large observational study. An innovative data-driven classification method was used to identify patient subgroups with distinct treatment trajectories (e.g., early-onset-high-dose). In our cohort, A. Groenman, PhD, found these trajectories to be clinically relevant for the development of substance use disorder (unpublished data, 2015). Moreover, treatment timing and dose have been found to moderate long-term stimulant treatment effects in the rat brain.[e.g.,22] In prior work, our group showed higher striatal BOLD-response to reward outcome in ADHD patients compared to controls.[18] In the current study, we hypothesized that patients who had received more intense treatment would show reduced striatal BOLD-response (i.e., more similar to controls) to reward outcome compared to those who had received less intense treatment. Second, we hypothesized that between-group differences in other brain regions, if any, would show a similar pattern.

Method

Participants

Participants with ADHD were selected from the family-based IMAGE-NeuroIMAGE cohort (2009-2012).[23] Children, adolescents, and young adults participated in diagnostic interviews, questionnaires, DNA collection, and an MRI session, taking place at two sites. Informed consent was signed by all participants ≥12 years old and all parents of participants <18 years old. The study was approved by the local ethical committees of each participating site. Inclusion criteria were: IQ≥70, age 8-30 years, no diagnosis of classical autism, learning difficulties, brain disorders, or genetic disorders, and no contra-indication for MRI scanning. ADHD diagnosis (any type) was confirmed in accordance with the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV),[24] operationalized as six or more symptoms on the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS[25]) and t>63 on the Conners parent-, teacher-, and/or self-rated ADHD scales,[26-28] rated while participants were off-medication. Five K-SADS symptoms were sufficient for diagnosis in participants age 16 or older, in line with DSM-5 revised criteria. The initial ADHD sample consisted of 269 participants. Functional MRI data were available for 124 patients (mean age=17.4 years, range 10-26 years).

Control participants were required to have no scores in the (sub)clinical range on any of the ADHD rating scales or interviews, no current or past psychiatric diagnosis or treatment, and no psychiatric diagnoses in first-degree relatives. The initial control sample consisted of 187 participants. Functional MRI data was available for 97 controls (mean age=17.0 years, range 10-23 years).

Stimulant treatment

History of psychoactive treatment was assessed using pharmacy prescription records containing delivery date, substance name, dose, quantity, and frequency of use for each delivery between date-of-birth and date-of-scan. In addition, patients and parents participated in face-to-face semi-structured

interviews to reconstruct lifetime treatment history. Self-report data was highly compatible with data derived from pharmacies (data not shown), with reliability estimates similar as those reported by Kuriyan et al.[29] Self-report data was used only when pharmacy data was incomplete. Stimulant intake in mg (immediate- and extended-release methylphenidate preparations, and dexamphetamine preparations) was reconstructed for each day between date-of-birth and date-of-scan. Daily intake in mg was averaged for every month of the participant's life. Stimulant start age, stop age, and lifetime cumulative stimulant dose were calculated from this reconstruction. A smooth generalized additive model curve was fitted to each participant's reconstruction, allowing estimation of three additional treatment parameters that were more sensitive to noise, i.e., treatment duration (estimated stop age minus estimated start age), treatment variability (standard deviation of the fitted curve), and the lifetime maximum dose. Treatment duration and cumulative stimulant dose were adjusted for current age. The use of non-stimulant psychoactive medication (e.g., risperidone, atomoxetine) was common, hence participants with a history of non-stimulant psychoactive medication were not excluded.

Community detection algorithm

The six stimulant treatment parameters (start age, stop age, total dose, estimated duration, estimated maximum daily dose, and estimated variability) were entered in an automated, optimization-based, weight-conserving community detection algorithm.[30] This algorithm, implemented in R, is intuitively interpretable and less computationally expensive as compared to e.g. finite mixture models. It categorizes participants into mutually exclusive communities (groups), segregating groups such that within-group positive/negative correlations are maximal while between-group correlations are minimal. The modularity statistic Q (range 0-1) quantifies the degree to which participants may be subdivided into clearly delineated groups. The algorithm terminates when Q no longer increases from one iteration to the next. Robustness of the optimal community structure was confirmed using non-parametric bootstrap procedures (eAppendix1).

The data-driven classification method produces more reliable results in larger samples, hence all participants with ADHD were included in this step (N=269). Stimulant-naive participants were *a priori* defined as a separate category (n=42, 15.1%). For stimulant-treated participants, the optimal solution yielded three treatment groups (Q=0.580; Table 1). The first group (n=111, 41.3%, 'early-and-intense') was characterized by early treatment onset, long duration, and a high maximum and total dose. The second group (n=96, 35.7%; 'late-and-moderate') was characterized by older age at treatment onset, shorter duration, and lower maximum and total dose. The third group (n=20, 7.4%; 'early-and-moderate') was characterized by early treatment onset, medium duration, and low maximum and total dose. As few participants were classified to the 'early-and-moderate' group or were stimulant-naive, 'early-and-intense'-*vs.*-'late-and-moderate' was our primary contrast of interest. As shown in Table 1, the 'early-and-intense' and 'late-and-moderate' groups differed in stimulant start age, treatment duration, variability, maximum dose, and total dose, but not in stop age.

Reward task

A modified version of the monetary incentive delayed task was performed in the scanner.[18] Participants were asked to respond as quickly as possible to a target by pressing a button. Before this target, a cue indicated the possibility of gaining a reward after a button press within a given time-window. Every trial ended with a feedback screen informing about the outcome of the current trial. Depending on the participants' performance, the response-window for a correct response was adapted in the next trial, resulting in an expected hit-rate of 33%. The experiment lasted 12 minutes, and a total of €5 could be gained. At the end of the experiment, the awarded money was paid to the participant. Compared with the original task, our version differed on two main aspects: hit-rate (33% versus 66%) and reward magnitude (€0.20 versus $5). The rationale behind these adaptations was firstly to increase the demands of the task with stronger task engagement as a result. Secondly, our adaptations aimed at meeting the practical constraints of our study. Considering that we limited ourselves to rewarded and neutral conditions,

rewarding participants according to the original task parameters would have led to disproportionate monetary rewards (approximately €80), which was a concern for us and our ethical review board. Reaction time reward sensitivity was calculated as the mean reaction time across non-rewarded trials minus the mean reaction time across rewarded trials, with higher values indicating higher sensitivity to reward.

Functional MRI processing and analyses

Acquisition parameters, preprocessing steps, and first-level analyses were identical to those in our previous publication[18] (eAppendix2). Second-level analyses for each task condition (reward anticipation and outcome) comprised both region of interest (ROI) and whole-brain analyses in FMRIB Software Library (FSL).[31] First, main task effects were identified in a one-sample t-test, with scanner, age, gender, and three motion parameters as regressors of no interest. For the ROI analyses, average parameter estimate was extracted for each participant from the (warped) task-activated voxels within a binary mask of the striatum (caudate, putamen, and accumbens). In a linear mixed effect regression model in SPSS,[32] striatal activation was predicted from treatment group (primary contrast: 'early-and-intense'-*vs.*-'late-and-moderate'; secondary contrasts: 'stimulant-naive'-*vs.*-'early-and-intense', 'stimulant-naive'-*vs.*-'late-and-moderate', 'stimulant-naive'-*vs.*-'early-and-moderate', 'early-and-moderate'-*vs.*-'early-and-intense', 'early-and-moderate'-*vs.*-'late-and-moderate'). Gender, scanner, age, and age^2 (to account for non-linear developmental trajectories of reward-related striatal activation[33]) were added as covariates, along with a random intercept per family to account for relatedness within the sample. Given our research question, alpha was adjusted for analyzing one primary and five secondary group contrasts in two task conditions (α=0.05/6/2=0.004). The same alpha was applied for all covariates included in the model (i.e., gender, age, scanner). Normalized first-level b-maps were entered into whole-brain second-level mixed effect analyses. Treatment group was entered as a predictor along with scanner, gender, age, and three movement parameters (Z_{VOXEL}>2.3; $\alpha_{CLUSTER}$=0.004).

Structural MR images were also acquired, to assess structural correlates of long-term functional changes, if any (eAppendix3).

Follow-up and sensitivity analyses

For each whole-brain significant cluster, average parameter estimate was extracted per participant for follow-up analyses in SPSS. Treatment groups were data-driven, hence not matched with regard to clinical and demographic variables. Potential confounders other than age and gender (i.e., IQ, SES, ADHD symptoms, ADHD-type, comorbidity, and history of non-stimulant psychoactive medication) were added to the model. Moreover, analyses were repeated within one-to-one age-, gender-, and ADHD symptom count-matched subsamples (n=25 per group).

To exclude acute withdrawal/rebound effects, each significant effect was re-estimated separately for participants who were on active stimulant treatment within two weeks prior to scanning and those who had ceased treatment more than two weeks prior to scanning.

Main reward task effects and case-control differences in the current cohort have previously been reported,[18] hence are not addressed here. For reference only, the control sample mean for each outcome measure was estimated in a covariate-only model.

Results

Sample characteristics

The ADHD sample consisted of 83 males (66.9%) and 41 females (33.1%), with an average age of 17.4 years (SD=3.0, range 10-26 years; Table 2). Of those, 51 participants were assigned to the 'early-and-intense' treatment group (46.8%), and 49 to the 'late-and-moderate' group (45.0%). Compared to the 'late-and-moderate' treatment group, the 'early-and-intense' group contained more males and more

participants on active stimulant treatment, and had more attention problems. The two groups did not differ with regard to age, socio-economic status, IQ, ADHD-type, hyperactivity/impulsivity symptoms, comorbidity, or history of non-stimulant medication. The control sample (n=97; mean age=17.0 years, SD=2.9, range 10-23 years) contained fewer males compared to the ADHD sample (44.3% *vs.* 66.9%; p=0.001). For the stimulant-naive (n=15) and 'early-and-moderate' (n=9) groups, see eAppendix4.

Reward processing

The striatum was activated by both task conditions (Figure 1). There were no differences in striatal BOLD-response between the 'early-and-intense' and 'late-and-moderate' treatment groups during reward anticipation ($Mean_{EARLY\&INTENSE}$=360.7, $Mean_{LATE\&MODERATE}$=394.8, $Mean_{CONTROL}$=299.7, p=0.784), or during reward outcome ($Mean_{EARLY\&INTENSE}$=362.1, $Mean_{LATE\&MODERATE}$=677.5, $Mean_{CONTROL}$=414.9; p=0.180).

Whole-brain analyses did not yield any clusters of significant difference between the 'early-and-intense' and the 'late-and-moderate' groups during reward anticipation. In the reward outcome condition, the 'late-and-moderate' group showed lower activity compared to the 'early-and-intense' group in a cluster located in the SMA, extending into the dorsal anterior cingulate cortex (dACC) and paracingulate gyrus (Figure 2; $Mean_{EARLY\&INTENSE}$=635.1, $Mean_{LATE\&MODERATE}$=-813.9, $Mean_{CONTROL}$=35.5, cluster size=8696 mm^3, B=-1449.0, $p_{CLUSTER}$<0.001). Gender (B=964.6, p=0.014), scanner (B=179.0, p=0.604), age (B=-285.8, p=0.087), and age^2 (B=153.8, p=0.087) were not associated with activation in this cluster, nor were any of the additional covariates (e.g., IQ, ADHD symptoms, non-stimulant treatment history, and comorbidity including substance use disorders) when added to the model while the effect of treatment history remained unchanged. Moreover, the pattern was consistently observed in past users ($Mean_{EARLY\&INTENSE}$=374.9, $Mean_{LATE\&MODERATE}$=-687.3) and current users ($Mean_{EARLY\&INTENSE}$=785.0, $Mean_{LATE\&MODERATE}$=-1323.6), and within the age-, gender-, and symptom-matched subsamples ($Mean_{EARLY\&INTENSE}$=721.5, $Mean_{LATE\&MODERATE}$=-395.5).

There was no behavioral (i.e., reaction time) difference in reward sensitivity between the 'early-and-intense' and 'late-and-moderate' groups ($Mean_{EARLY\&INTENSE}$=35.0ms, $Mean_{LATE\&MODERATE}$=29.4ms, p=0.559, for reference: $Mean_{CONTROL}$=25.7ms). Moreover, reaction time reward sensitivity was not associated with striatal activity during reward anticipation (Pearson r=0.173, p=0.055) or reward outcome (Pearson r=0.014, p=0.879), nor with activity within the SMA/dACC cluster (Pearson r=0.177, p=0.050).

There were no structural brain differences between the two groups. For findings involving the 'early-and-moderate' and stimulant-naive groups, see eAppendix4.

Discussion

In a large sample of children, adolescents and young adults with ADHD, we investigated whether characteristics of stimulant treatment history were associated with brain activation patterns during reward processing while off medication. Stimulant treatment history was not associated with BOLD-response to reward anticipation or outcome in the striatum. In the SMA/dACC, individuals with a history of moderate treatment showed lower activity during reward outcome compared to those with a history of intense treatment. While activity in the moderately treated group was reduced compared to controls, activity in the intensely treated group was higher compared to controls. Our findings thus suggest compensatory SMA/dACC recruitment in individuals with a history of intense stimulant treatment. The effect is likely driven by treatment duration and dose rather than recency of treatment discontinuation, since stop age did not differ between the two groups.

Higher striatal BOLD-response to reward outcome has consistently been reported in ADHD.[e.g.,17,18] As such changes have been shown to disappear after stimulant administration,[16,34] we had hypothesized that participants with a history of intense treatment would show lower striatal BOLD-response to reward outcome compared to those with a history of less intense treatment. We found no evidence for such an effect. Moreover, there was no association between treatment history and striatal activity during reward anticipation. Our findings may indicate that the acute changes in striatal activity in

response to stimulants do not translate into lasting functional changes in this region during reward processing. This finding is consistent with Stoy et al[12] who, in a small adult sample, also reported no changes in striatal activation during reward outcome after childhood stimulant treatment.

We found a large cluster of lower activity during reward outcome in the moderately treated subgroup compared to the intensely treated subgroup, located in the bilateral SMA and dACC, extending into the precuneus and posterior cingulate cortex. Dorsal and mid-cingulate regions project to the ventral striatum, and are important for monitoring incentive-based behavioral responses.[35,36] Hypo-activation has previously been reported in medication-naive ADHD patients during reward outcome.[37] Acute stimulant effects in the SMA/dACC during reward processing have been reported as well,[16] although most fMRI studies of reward reported no acute stimulant effects in this region.[e.g.,21,34]

Lower activity in the SMA/dACC in ADHD patients has also been associated with cognitive processes other than reward processing. Higher SMA/dACC activation may represent recruitment of a cognitive process enhancing feedback-based decision-making, even when a motor response is not required,[38,39] as was the case in the reward outcome phase of our task. ADHD patients have shown lower SMA activity when selection of a non-habitual response was required.[13,40] Higher SMA/dACC, PCC, and precuneus activity has been reported after a single dose of stimulants during tasks requiring feedback-based modulation of motor responses,[41-43] but acute effects in the opposite direction have also been reported.[10,44] Enhanced cognitive decision-making upon reward in intensely-treated individuals is consistent with the lower rate of substance use disorder in this group (A. Groenman, PhD, unpublished data, 2015), although the difference in substance use disorder rate in the current (smaller) fMRI sample was not significant. Summarizing, higher SMA/dACC activity may indicate enhanced cognitive decision-making following reward after early and high-dose stimulant treatment. Note that this proposition is not supported in behavioral data, as our paradigm required no response following reward outcome.

Alternatively, higher SMA/dACC activity may represent increased salience network activity, enhancing attention allocation to emotional, rewarding, or surprising events.[45] Stimulant-induced improvement in cognitive performance has been shown to be mediated by enhanced salience.[46,47]

Stimulant treatment history may be associated with greater task focus. Yet, increased task focus may be expected to occur throughout the task as opposed to during the outcome phase only, and may result in improved task performance which we did not observe. Finally, higher SMA/dACC activity may entail enhanced 'readiness to act' upon reward outcome, as the SMA is embedded in the task-positive motor network.[48] However, we found no association between SMA/dACC activation and reaction times.

The current study has several strengths. First, only a handful of prior studies investigated functional rather than anatomical long-term neural changes in relation to stimulant treatment in ADHD. Of those, the current sample is by far the largest. Second, the data-driven classification of participants with ADHD based on multiple treatment characteristics is novel and clinically relevant. The current study has limitations as well. Long-term treatment effects can only be studied observationally. Although findings have been statistically adjusted for group differences, confounding by indication could not be excluded. Moreover, few participants were stimulant-naïve (in accordance with high prescription rates), and data-driven classification of stimulant-treated participants yielded unbalanced groups. This allowed powerful analysis of participants in the two largest groups, but restricted analyses of stimulant-naive participants and those with early-and-moderate treatment. Finally, no data was collected regarding behavioral treatment which, according to guidelines, should be offered in conjunction with pharmacological treatment; hence, pharmacological and behavioral treatment effects cannot be distinguished in our study. The recruitment of compensatory cognitive control areas may reflect the application of cognitive strategies learned during behavioral treatment.

We conclude that ADHD patients with a history of early-onset high-dose stimulant treatment showed more SMA/dACC activation during reward outcome, compared to those with a history of late-onset moderate-dose stimulant treatment. Higher SMA/dACC activity may represent a compensatory mechanism of enhanced higher-level processing of reward information in the intensely treated group. Stimulant treatment history was not associated with striatal BOLD-response to reward processing. Understanding long-term risk and benefits of stimulant treatment could be further enhanced by evaluating functional rather than neuroanatomical brain changes in future studies.

Clinical points

- Stimulant treatment is regarded a safe and effective treatment for ADHD symptoms, yet their long-term effects on brain activation patterns in children and adolescents are largely unknown.
- Early and intense stimulant treatment may result in increased activation of cognitive control areas during rewarding situations, even when patients are non-medicated at that time.

References

1. Trip, AM, Visser, ST, Kalverdijk, LJ, et al. Large increase of the use of psycho-stimulants among youth in the Netherlands between 1996 and 2006. *British Journal of Clinical Pharmacology.* 2009;67(4):466–468.
2. Van de Loo-Neus, GHH, Rommelse, N, & Buitelaar, JK. To stop or not to stop? How long should medication treatment of attention-deficit/hyperactivity disorder be extended? *European Neuropsychopharmacology,* 2011;21(8):584–599.
3. Jensen, PS, Arnold, LE, Swanson, JM, et al. 3-year follow-up of the NIMH MTA study. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2007;46(8):989–1002.
4. Molina, BSG, Hinshaw, SP, Swanson, JM, et al. The MTA at 8 years: prospective follow-up of children treated for combined-type ADHD in a multisite study. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2009;48(5):484–500.
5. Frodl, T, & Skokauskas, N. Meta-analysis of structural MRI studies in children and adults with attention-deficit/hyperactivity disorder indicates treatment effects. *Acta Psychiatrica Scandinavica.* 2012;125(2):114–126.
6. Nakao, T, Radua, J, Rubia, K, et al. Gray matter volume abnormalities in ADHD: voxel-based meta-analysis exploring the effects of age and stimulant medication. *American Journal of Psychiatry.* 2011;168(11):1154–1163.
7. Shaw, P, DeRossi, P, Watson, B, et al. Mapping the development of the basal ganglia in children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2014;53(7):780–789.e11.
8. Greven, CU, Bralten, J, Mennes, M, et al. Developmentally stable whole-brain volume reductions and developmentally sensitive caudate and putamen volume alterations in those with attention-deficit/hyperactivity disorder and their unaffected siblings. *JAMA Psychiatry.* 2015;72(5):490–499.

9. Schweren, LJS, Hartman, CA, Heslenfeld, DJ, et al. Thinner medial temporal cortex in adolescents with attention-deficit/hyperactivity disorder and the effects of stimulants. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2015;54(8):660–667.
10. Rubia, K, Alegria, AA, Cubillo, AI, et al. Effects of stimulants on brain function in attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *Biological Psychiatry.* 2014;76(8):1–15.
11. Schlochtermeier, L, Stoy, M, Schlagenhauf, F, et al. Childhood methylphenidate treatment of ADHD and response to affective stimuli. *European Neuropsychopharmacology.* 2011;21(8):646–654.
12. Stoy, M, Schlagenhauf, F, Schlochtermeier, L, et al. Reward processing in male adults with childhood ADHD-a comparison between drug-naïve and methylphenidate-treated subjects. *Psychopharmacology*. 2011;215(3):467–481.
13. Hart, H, Radua, J, Nakao, T, et al. Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: exploring task-specific, stimulant medication, and age effects. *JAMA Psychiatry*. 2013;70(2):185–198.
14. Fusar-Poli, P, Rubia, K, Rossi, G, et al. Striatal dopamine transporter alterations in ADHD: Pathophysiology or adaptation to psychostimulants? A meta-analysis. *American Journal of Psychiatry*. 2012;169(3):264–272.
15. Ludolph, AG, Kassubek, J, Schmeck, K, et al. Dopaminergic dysfunction in attention-deficit/hyperactivity disorder (ADHD), differences between pharmacologically treated and never treated young adults: a 3,4-dihdroxy-6-[18F]fluorophenyl-l-alanine PET study. *NeuroImage.* 2008;41(3):718–727.
16. Aarts, E, van Holstein, M, Hoogman, M, et al. Reward modulation of cognitive function in adult attention-deficit/hyperactivity disorder: a pilot study on the role of striatal dopamine. *Behavioural Pharmacology*. 2015;26(1-2):227–240.

17. Paloyelis, Y, Mehta, M, Faraone, S, et al. Striatal sensitivity during reward processing in attention-deficit/hyperactivity disorder (ADHD). *Journal of the American Academy of Child and Adolescent Psychiatry*. 2012;51(7):997–1003.
18. von Rhein, D, Cools, R, Zwiers, MP, et al. Increased neural responses to reward in adolescents and young adults with attention-deficit/hyperactivity disorder and their unaffected siblings. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2015;54(5):394–402.
19. Peterson, BS, Potenza, MN, Wang, Z, et al. An fMRI study of the effects of psychostimulants on default-mode processing during Stroop task performance in youths with ADHD. *American Journal of Psychiatry*. 2009;166(11):1286–1294.
20. Prehn-Kristensen, A, Krauel, K, Hinrichs, H, et al. Methylphenidate does not improve interference control during a working memory task in young patients with attention-deficit/hyperactivity disorder. *Brain Research*. 2011;1388:56–68.
21. Rubia, K, Halari, R, Cubillo, A, et al. Methylphenidate normalises activation and functional connectivity deficits in attention and motivation networks in medication-naïve children with ADHD during a rewarded continuous performance task. *Neuropharmacology*. 2009;57(7-8):640–652.
22. van der Marel, K, Klomp, A, Meerhoff, GF, et al. Long-term oral methylphenidate treatment in adolescent and adult rats: differential effects on brain morphology and function. *Neuropsychopharmacology*. 2014;39(2):263–273.
23. von Rhein, D, Mennes, M, van Ewijk, H, et al. The NeuroIMAGE study: a prospective phenotypic, cognitive, genetic and MRI study in children with attention-deficit/hyperactivity disorder. Design and descriptives. *European Child and Adolescent Psychiatry*. 2015;24(3):265-281.
24. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Arlington, VA: American Psychiatic Publishing Inc. 2013.
25. Kaufman, J, Birmaher, B, Brent, D, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1997;36(7):980–988.

26. Conners, CK, Erhardt, D, & Sparrow, AP. *Conner's Adult ADHD Rating Scales: CAARS.* North Tonawanda, NY: Multi-Health Systems. 1999.
27. Conners, CK, Sitarenios, G, Parker, JDA, et al. Revision and restandardization of the Conners' Teacher Rating Scale (CTRS-R): factor structure, reliability, and criterion validity. *Journal of Abnormal Child Psychology.* 1998;26(4):279–291.
28. Conners, CK, Sitarenios, G, Parker, JDA, et al. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. *Journal of Abnormal Child Psychology.* 1998;26(4):257–268.
29. Kuriyan, AB, Pelham, WE, Molina, BSG, et al. Concordance between parent and physician medication histories for children and adolescents with attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology.* 2014;24(5):269–274.
30. Rubinov, M, & Sporns, O. Weight-conserving characterization of complex functional brain networks. *NeuroImage.* 2011;56(4):2068–2079.
31. Smith, SM, Jenkinson, M, Woolrich, MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage.* 2004;23(SUPPL.1):208–219.
32. IBM. *IBM SPSS Statistics for Windows*. Armonk: NY: IBM Corp. 2011.
33. Braams, BR, van Duijvenvoorde, AC,, Peper, JS, et al. Longitudinal changes in adolescent risk-taking: a comprehensive study of neural responses to rewards, pubertal development, and risk-taking behavior. *Journal of Neuroscience.* 2015;35(18):7226-7238.
34. Knutson, B, Bjork, JM, Fong, GW, et al. Amphetamine modulates human incentive processing. *Neuron.* 2004;43(2):261–269.
35. Haber, SN, & Knutson, B. The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology*. 2010;35(1):4–26.
36. Shima, K, & Tanji, J. Role for cingulate motor area cells in voluntary movement selection based on reward. *Science.* 1998;282(5392):1335–1338.

37. Carmona, S, Hoekzema, E, Ramos-Quiroga, JA, et al. Response inhibition and reward anticipation in medication-naïve adults with attention-deficit/hyperactivity disorder: a within-subject case-control neuroimaging study. *Human Brain Mapping*. 2012;33(10):2350–2361.
38. Ullsperger, M, & von Cramon, DY. Error monitoring using external feedback: specific roles of the habenular complex, the reward system, and the cingulate motor area revealed by functional magnetic resonance imaging. *The Journal of Neuroscience*. 2003;23(10):4308–4314.
39. Vassena, E, Cobbaert, S, Andres, M, et al. Unsigned value prediction-error modulates the motor system in absence of choice. *NeuroImage.* 2015;122:73–79.
40. Suskauer, SJ, Simmonds, DJ, Fotedar, S, et al. Functional magnetic resonance imaging evidence for abnormalities in response selection in attention-deficit/hyperactivity disorder: differences in activation associated with response inhibition but not habitual motor response. *Journal of Cognitive Neuroscience.* 2008;20(3):478–493.
41. Bush, G, Spencer, TJ, Holmes, J, et al. Functional magnetic resonance imaging of methylphenidate and placebo in attention-deficit/hyperactivity disorder during the multi-source interference task. *Archives of General Psychiatry*. 2008;65(1):102–114.
42. Cubillo, A, Smith, AB, Barrett, N, et al. Shared and drug-specific effects of atomoxetine and methylphenidate on inhibitory brain dysfunction in medication-naive ADHD boys. *Cerebral Cortex.* 2014;24(1):174-185.
43. Pliszka, SR, Liotti, M, Bailey, BY, et al. Electrophysiological effects of stimulant treatment on inhibitory control in children with attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology*. 2007;17(3):356–366.
44. Ivanov, I, Liu, X, Clerkin, S, et al.Methylphenidate and brain activity in a reward/conflict paradigm: role of the insula in task performance. *European Neuropsychopharmacology*. 2014;24(6):897–906.
45. Menon, V. *Salience Network.* Brain Mapping (Vol. 2). Elsevier Inc. 2015
46. Ter Huurne, N, Fallon, SJ, van Schouwenburg, M, et al. Methylphenidate alters selective attention by amplifying salience. *Psychopharmacology*. 2015;232(23):4317-4323.

47. Volkow, ND, Wang, GJ, Fowler, JS, et al. Evidence that methylphenidate enhances the saliency of a mathematical task by increasing dopamine in the human brain. *American Journal of Psychiatry*. 2004;161(7):1173–1180.

48. Jolles, DD, van Buchem, MA, Crone, EE, et al. A comprehensive study of whole-brain functional connectivity in children and young adults. Cerebral Cortex. 2011;21(2):385–391.